Edaravone with and without .6 Mg/Kg Alteplase within 4.5 Hours after Ischemic Stroke: A Prospective Cohort Study (PROTECT4.5)

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Background: Edaravone is widely used to treat acute ischemic stroke (AIS) within 24 hours of onset. We aimed to evaluate current edaravone treatment practices and the efficacy and safety of edaravone used with recombinant tissue plasminogen activator (tPA) in AIS patients within 4.5 hours of onset. The results were compared with those of the Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Registry (SITS-ISTR) study. *Methods:* PROTECT4.5 was a prospective observational study conducted from April 2010 to March 2013 in Japan. The primary end points were favorable outcomes (modified Rankin Scale score [mRS] 0-1) at 3 months after onset and incidence of symptomatic intracranial hemorrhage (sICH) within 36 hours of treatment. For comparison with SITS-ISTR, patients were categorized based on the time from onset to treatment (within 3 hours of and 3-4.5 hours after onset) and baseline National Institutes of Health Stroke Scale score (NIHSS). *Results:* Among the 11,384 registered patients, 11,126 and 8274 patients were included in the safety and efficacy analysis populations, respectively. The proportions of patients with mRS 0-1 receiving edaravone alone and edaravone + tPA were 51.3% (95% confidence interval, 49.7%-52.8%) and 39.0% (37.6%-40.5%), respectively. The incidence of sICH within 36 hours after tPA treatment (edaravone + tPA group) was 1.6% (1.3%-2.0%). When compared with the SITS-ISTR results, those treated with edaravone + tPA appeared to show better outcomes in patients with NIHSS score ≥16. *Conclusions:* The efficacy and safety of edaravone combined with tPA and administered within 4.5 hours of AIS onset were demonstrated with

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Author contributions: Drs Yamaguchi and Tanahashi supervised the study, and contributed to the interpretation of the results. Mr Awano contributed to the interpretation of the results. Mr Matsuda contributed to the study design, data processing, and statistical analysis. All authors contributed to manuscript preparation and have approved the final draft.

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numerically lower incidence of sICH and better outcomes. **Key Words:** Acute ischemic stroke—edaravone—Japan—prospective observational study—recombinant tissue plasminogen activator—symptomatic intracranial hemorrhage.

Introduction

Edaravone (EDV), a free radical scavenger developed in Japan, strongly suppresses the peroxidation reaction of lipids in the arachidonate cascade,[1] which is enhanced by cerebral ischemia, and inhibits vascular endothelial cell damage, cerebral edema, and delayed neuronal death.[2] Based on a Japanese study of acute ischemic stroke (AIS) patients,[3] edaravone was approved in Japan by the Ministry of Health, Labour and Welfare for the treatment of ischemic stroke within 24 hours of onset, and is widely used for AIS within 24 hours of onset following the guidelines for stroke management.[4-6]

The efficacy and safety of intravenous recombinant tissue plasminogen activator (tPA) were shown up to 4.5 hours after onset in the European Cooperative Acute Stroke Study (ECASS-III)[7] and in a large-scale cohort study (Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Registry [SITS-ISTR]).[8] Subsequently, the European Stroke Organization recommended that the therapeutic time window (TTW) of tPA should be extended to 4.5 hours after onset.[9] Thereafter, the American Heart Association and the American Stroke Association made similar revisions.[10]

In 2005, alteplase, a tPA, was approved in Japan at a dose of .6 mg/kg, which is lower than that used in other countries (.9 mg/kg), based on the results of the Japan Alteplase Clinical Trial.[11] In 2013, the TTW was extended to "within 4.5 hours of symptom onset,"[12] in response to the ECASS-III[7] and SITS-ISTR results.[8]

PROTECT4.5 (Postmarketing Registry On Treatment with Edaravone in acute Cerebral infarction by the Time window of 4.5 h) aimed to evaluate the current practices in edaravone treatment in patients with AIS and the efficacy and safety of edaravone used with tPA (edaravone + tPA) at .6 mg/kg, when administered within 4.5 hours of onset. In an additional post-hoc analysis that was not predefined, the efficacy and safety of edaravone + tPA are compared with the results of SITS-ISTR (tPA alone).[13]

Methods

PROTECT4.5 was a prospective cohort study performed in clinical practice for the postmarketing surveillance of edaravone conducted by Mitsubishi Tanabe Pharma Corporation (Osaka, Japan). PROTECT4.5 was conducted in accordance with the Good Postmarketing Study Practice guidelines specified by the Ministry of Health, Labour and Welfare at 1121 institutions specializing in the treatment of AIS in Japan (Supplementary File S1). The targeted sample size was 10,000 patients, and the study was conducted from April 2010 to March 2013. The trial is registered under the number UMIN000009227.

The inclusion criteria were as follows: AIS patients receiving EDV within 4.5 hours of onset, a consciousness level of 0-30 by the Japan Coma Scale,[14] and weakness in the upper or lower limbs (hemiparesis or hemiplegia). The exclusion criteria were baseline serum creatinine level >1.5 mg/dL, history of hypersensitivity to components of EDV, ineligibility to participate in the study as judged by the attending physician because of the presence of severe liver disease (e.g., hepatic cirrhosis) or heart disease (e.g., congestive heart failure) requiring hospitalization, infection-related complications requiring administration of antibiotics, or other reasons; modified Rankin Scale score [mRS] ≥2 before onset; severe neurologic deficit (National Institutes of Health Stroke Scale [NIHSS]: ≥23) before EDV treatment; history of cerebral infarction within 3 months; complicated with intracranial hemorrhage; and showing marked improvement in neurologic symptoms and signs, with a high probability of transient ischemic attack. Patients were registered within 6 days after onset.

Patients were treated with edaravone alone or edaravone + tPA depending on their clinical condition and the time of arrival at the hospital. A 30-mg dose of edaravone was diluted with saline and administered twice daily in the morning and late afternoon by intravenous infusion for 30 minutes, for several days. The tPA was administered according to the dosage regimen approved in Japan (10% of a dose [.6 mg/kg] of tPA was given by rapid intravenous injection; the rest was given by intravenous infusion for 1 hour).

The primary end point measures were favorable outcomes (mRS 0-1) at 3 months after onset and incidence of symptomatic intracranial hemorrhage (sICH) within 36 hours of treatment. When comparing the incidence of sICH between those in the present study who received treatment with edaravone + tPA (the PROTECT4.5-tPA population) and SITS-ISTR, the incidence of sICH after tPA treatment was defined as follows: First, sICH within 36 hours after tPA treatment was defined according to the SITS-Monitoring Study (SITS-MOST) definition.[15] Second,

sICH within 7 days after tPA treatment was defined according to the ECASS-II definition.[16]

Statistical Analysis

The proportion and the 95% confidence interval of patients with mRS 0-1 and incidence of sICH were calculated. PROTECT4.5 did not include patients treated with tPA alone. To compare our results with those of SITS-ISTR in which patients were treated with tPA alone,[13] a dataset for the PROTECT4.5-tPA population (including only patients with a baseline NIHSS score ≤25 and aged 18-80 years) was prepared to adjust for baseline characteristics and was divided into two groups based on the time from onset to tPA treatment: one group included patients treated within 3 hours of onset and the other included those treated during the period of 3-4.5 hours after onset. The Pearson chi-square test was used to compare the proportion of patients with mRS 0-1 and mRS 6 stratified by baseline NIHSS and the incidence of sICH within 36 hours in the PROTECT4.5-tPA population, and the proportions and incidences stated in a figure from the article by Ahmed et al from SITS-ISTR.[13] This analysis was performed using values obtained from the article, not from the authors of the SITS-ISTR study. Statistical significance was considered as a two-tailed probability of less than .05 without any correction based on a multiple comparison approach. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Results

Disposition of Patients

A total of 11,384 patients were registered. Among them, 11,126 patients (847 centers) from whom case report forms were available were evaluated as the safety analysis population (SAFP). Of the 11,126 patients, 8274 patients in whom the mRS was evaluated at 3 months after onset were used for the efficacy analysis population (EFFP). The number of patients whose baseline characteristics were adjusted for comparison with SITS-ISTR was 8052 for the safety evaluation (modified SAFP) and 6130 for the efficacy evaluation (modified EFFP) (Fig 1). Some patients with a baseline NIHSS score ≥23 were registered, despite this being an exclusion criterion.

Patient Baseline Characteristics

The median age was 74 years in patients receiving edaravone alone or edaravone + tPA. The median NIHSS score was 6 and 13 in patients receiving edaravone alone and edaravone + tPA, respectively (Table 1). In most patients receiving edaravone alone and edaravone + tPA, the NIHSS score was within 0-5 and 6-20, respectively (Fig 2, A).

Efficacy and Safety

The proportion of patients with mRS 0-1 at 3 months after onset was 51.3% in those receiving edaravone alone and 39.0% in those receiving edaravone + tPA. The

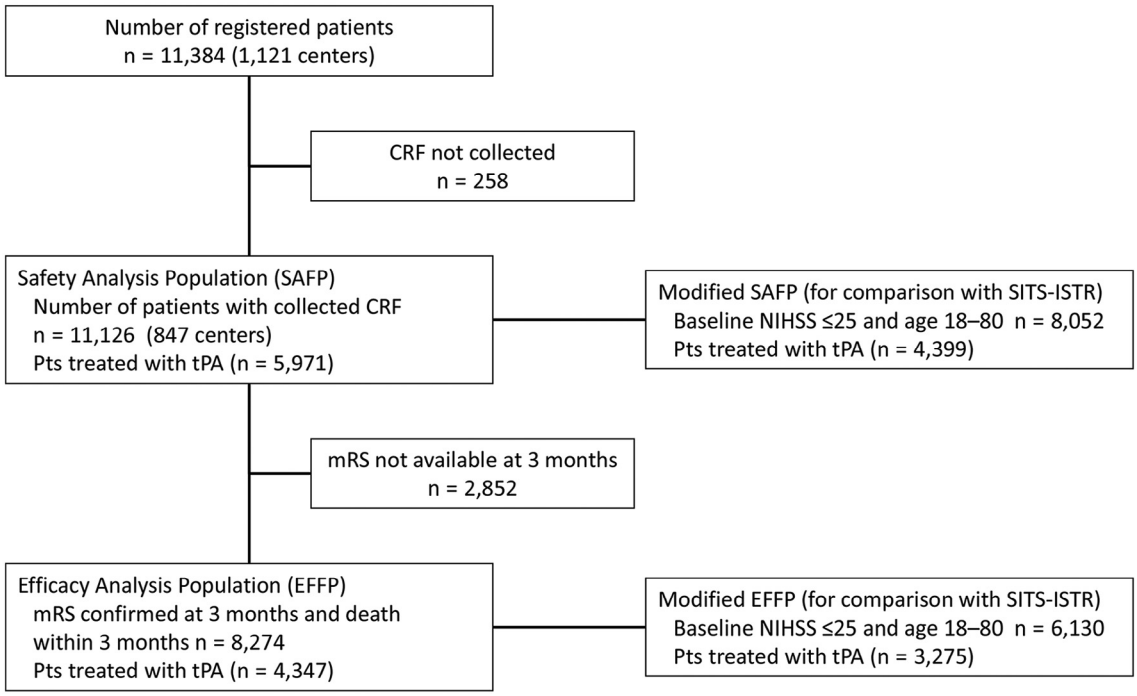

Figure 1. *Disposition of patients. Abbreviations: CRF, case report form; mRS, modified Rankin Scale score; NIHSS, National Institutes of Health Stroke Scale score; Pts, patients; SITS-ISTR, Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Registry; tPA, recombinant tissue plasminogen activator.*

Table 1. *Patient baseline characteristics (safety analysis population)*

Characteristics	Edaravone alone N = 5155	Edaravone + tPA N = 5971
Age, years	74 (65-81)	74 (66-81)
Sex, women	1874 (36.4)	2275 (38.1)
Prestroke independence, mRS 0-1	5039 (97.7)	5891 (98.7)
Concomitant disease		
Hypertension	3131 (60.7)	3522 (59.0)
Diabetes mellitus	1005 (19.5)	1042 (17.5)
Atrial fibrillation	1334 (25.9)	2038 (34.1)
Ischemic heart disease	400 (7.8)	434 (7.3)
Heart failure	250 (4.8)	345 (5.8)
Valvular disease	134 (2.6)	167 (2.8)
Previous stroke <3 months before	16 (.3)	4 (.1)
Baseline NIHSS	6 (3-12)	13 (8-18)
Subtype of ischemic stroke		
Cardioembolic	1878 (36.4)	3414 (57.2)
Atherothrombotic	1589 (30.8)	1577 (26.4)
Lacunar	1310 (25.4)	570 (9.5)
Others	376 (7.3)	408 (6.8)
Dosage periods of edaravone (days)	9 (7-14)	9 (7-14)
Time from onset to edaravone treatment (min)	180 (120-210)	120 (90-165)
Time from onset to tPA treatment (min)	–	137 (114-165)
Treatment with antiplatelets before onset	1234 (23.9)	1279 (21.4)
Treatment with anticoagulants before onset	598 (11.6)	645 (10.8)

Abbreviations: mRS, modified Rankin Scale score; NIHSS, National Institutes of Health Stroke Scale score; tPA, recombinant tissue plasminogen activator.

Data are presented as median (interquartile range) or N (%).

incidence of sICH within 36 hours after edaravone treatment was .5% in patients receiving edaravone alone and 1.6% in those receiving edaravone + tPA (Table 2).

Comparison with SITS-ISTR: A Post-Hoc Analysis

Baseline Characteristics (PROTECT4.5-tPA Population)

The baseline characteristics of patients in the PROTECT4.5-tPA population divided into two groups by the time from onset to tPA treatment (within 3 hours and 3-4.5 hours) are shown in Table 3. In both study groups, approximately 30% of the patients had NIHSS scores before treatment of 6-10 (Fig 2, B,C).

Distributions of the mRS (PROTECT4.5-tPA and SITS-ISTR Populations)

Figure 3A,B shows the mRS at 3 months after onset in the PROTECT4.5-tPA and SITS-ISTR populations, divided into two groups based on the time from onset to tPA treatment (within 3 hours and 3-4.5 hours) and stratified by baseline NIHSS scores (≤5, 6-10, 11-15, 16-20, and 21-25). Among patients with NIHSS scores of 16-20 or 21-25 in the 3-hour group, the proportion of patients with mRS 0-1 was significantly higher in those receiving edaravone + tPA (PROTECT4.5-tPA) than in those receiving tPA alone (SITS-ISTR) (both $P < .0001$). Among patients with NIHSS scores of 11-15, 16-20, or 21-25 in the 3-hour group, the death rate was significantly lower in PROTECT4.5-tPA than in SITS-ISTR (all $P < .0001$).

Incidence of sICH (PROTECT4.5-tPA and SITS-ISTR Populations)

The incidences of sICH within 36 hours (SITS-MOST definition) in the PROTECT4.5-tPA and SITS-ISTR populations were 1.5% and 1.7%, respectively, in the 3-hour group, and 1.5% and 2.2%, respectively, in the 3–4.5-hour group. The incidences of sICH within 7 days (ECASS-II definition) in the PROTECT4.5-tPA and SITS-ISTR populations were 1.8% and 4.8%, respectively, in the 3-hour group, and 3.0% and 5.3%, respectively, in the 3–4.5-hour group. The incidence of sICH based on the ECASS-II definition in the 3-hour group was significantly lower in PROTECT4.5-tPA than in SITS-ISTR ($P < .0001$) (Fig 3, C,D).

Discussion

Because there was no control group for the edaravone alone group, we cannot make any comments on the

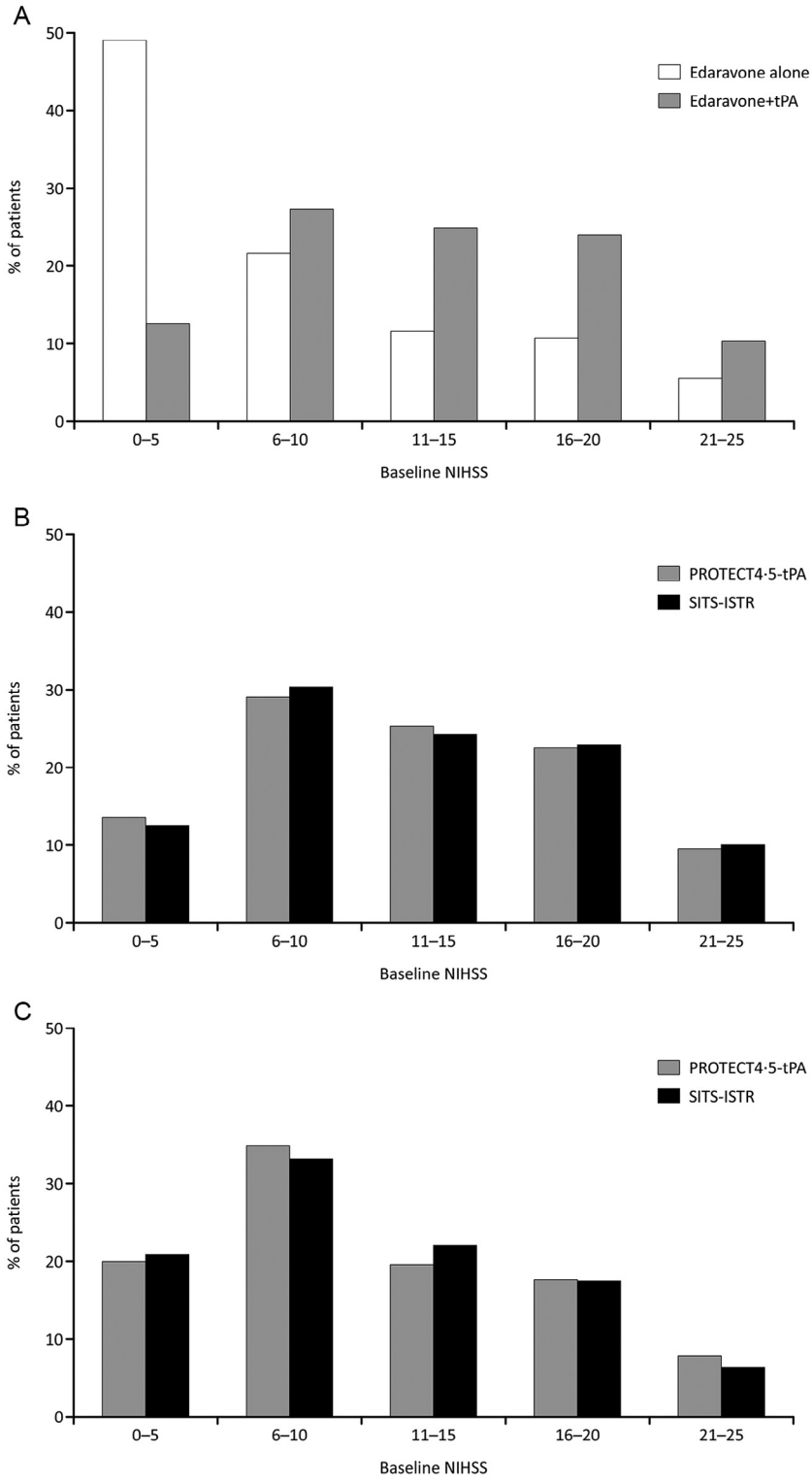

Figure 2. *Distribution of patients based on the NIHSS: (A) efficacy analysis population, (B) modified efficacy analysis population within 3 hours of onset, and (C) modified efficacy analysis population 3-4.5 hours after onset. Abbreviations: NIHSS, National Institutes of Health Stroke Scale score; SITS-ISTR, Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Registry; tPA, recombinant tissue plasminogen activator.*

efficacy and safety of edaravone as a neuroprotective agent. Data showing better outcomes in the edaravone alone group were due to the low baseline NIHSS scores in this group of patients. Most of the patients who received treatment during the period of 3-4.5 hours after onset were treated with edaravone alone because the registration period after the extension of the TTW was very short.

Edaravone + tPA showed more favorable outcomes (mRS 0-1) than another Japanese clinical study of tPA with or without edaravone, the Japan post-marketing alteplase

Table 2. *Overall efficacy and safety of edaravone*

	Edaravone alone	Edaravone + tPA
Efficacy analysis population	N = 3927	N = 4347
mRS at 3 months after onset		
0	1005 (25.6)	901 (20.7)
1	1008 (25.7)	795 (18.3)
0-1	2013 (51.3; 49.7-52.8)	1696 (39.0; 37.6-40.5)
2	559 (14.2)	594 (13.7)
3	318 (8.1)	452 (10.4)
4	492 (12.5)	794 (18.3)
5	288 (7.3)	450 (10.4)
6	257 (6.5)	361 (8.3)
Safety analysis population	N = 5155	N = 5971
Adverse events	598 (11.6; 10.7-12.5)	1091 (18.3; 17.3-19.3)
Intracranial hemorrhage	175 (3.4; 2.9-3.9)	530 (8.9; 8.2-9.6)
All sICH	54 (1.0; .8-1.4)	146 (2.4; 2.1-2.9)
sICH within 36 hours after edaravone treatment	26 (.5; .3-.7)	96 (1.6; 1.3-2.0)
sICH within 36 hours after tPA treatment	–	98 (1.6; 1.3-2.0)
Severe adverse events	368 (7.1; 6.5-7.9)	662 (11.1; 10.3-11.9)
Fatal adverse events	154 (3.0; 2.5-3.5)	218 (3.7; 3.2-4.2)
Edaravone-related adverse reactions	206 (4.0; 3.5-4.6)	349 (5.8; 5.3-6.5)

Abbreviations: mRS, modified Rankin Scale score; sICH symptomatic intracranial hemorrhage; tPA, recombinant tissue plasminogen activator. Data are N (%; 95% confidence interval).

registration study (J-MARS),[16] and a numerically lower incidence of sICH; therefore, the efficacy and safety of edaravone + tPA were demonstrated. In a post-hoc analysis, for patients with NIHSS scores ≥16 in the 3-hour group, the proportion of patients having favorable outcomes was significantly higher, and for patients with NIHSS scores ≥11 in the 3-hour group, the death rate was significantly lower among patients receiving edaravone + tPA (PROTECT4.5-tPA) than in those receiving tPA-alone (SITS-ISTR) ($P < .0001$, respectively). Although no complete

Table 3. *Baseline characteristics of the PROTECT4.5-tPA and SITS-ISTR populations*

	Within 3 hours of onset				3-4.5 hours after onset			
	PROTECT4.5-tPA		SITS-ISTR		PROTECT4.5-tPA		SITS-ISTR	
	N = 4065		N = 25,279		N = 334		N = 4056	
	Edaravone + tPA		tPA alone		Edaravone + tPA		tPA alone	
Age, years	70	63-75	68	58-74	70	65-75	67	57-74
Sex, women	1260/4065	31.0%	8546/21,566	39.6%	115/334	34.4%	1020/2376	42.9%
mRS 0-1 before stroke	4029/4065	99.1%	19,377/20,931	92.6%	330/334	98.8%	2089/2277	91.7%
Hypertension	2294/4065	56.4%	12,806/21,149	60.6%	209/334	62.6%	1416/2324	60.9%
Diabetes mellitus	757/4065	18.6%	3369/21,273	15.8%	71/334	21.3%	387/2344	16.5%
Atrial fibrillation	1243/4065	30.6%	4763/21,069	22.6%	93/334	27.8%	494/2334	21.2%
Heart failure	175/4065	4.3%	1611/21,181	7.6%	14/334	4.2%	184/2334	7.9%
Previous stroke ≤3 months before	4/4065	.1%	2213/21,314	10.4%	0/334	0%	257/2357	10.9%
Baseline NIHSS	12	8-17	12	7-17	10	6-16	10	6-15
Time from onset to tPA treatment (min)	133	110-157	140	114-165	210	190-237	205	190-229

Abbreviations: mRS, modified Rankin Scale score; NIHSS, National Institutes of Health Stroke Scale score; SITS-ISTR, Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Registry; tPA, recombinant tissue plasminogen activator.

Data are presented as median, interquartile range or N, %. For comparison with SITS-ISTR, a dataset of PROTECT4.5 (the PROTECT4.5-tPA population including only patients with a baseline NIHSS score ≤25 and aged 18-80 years) was prepared to adjust for baseline characteristics.

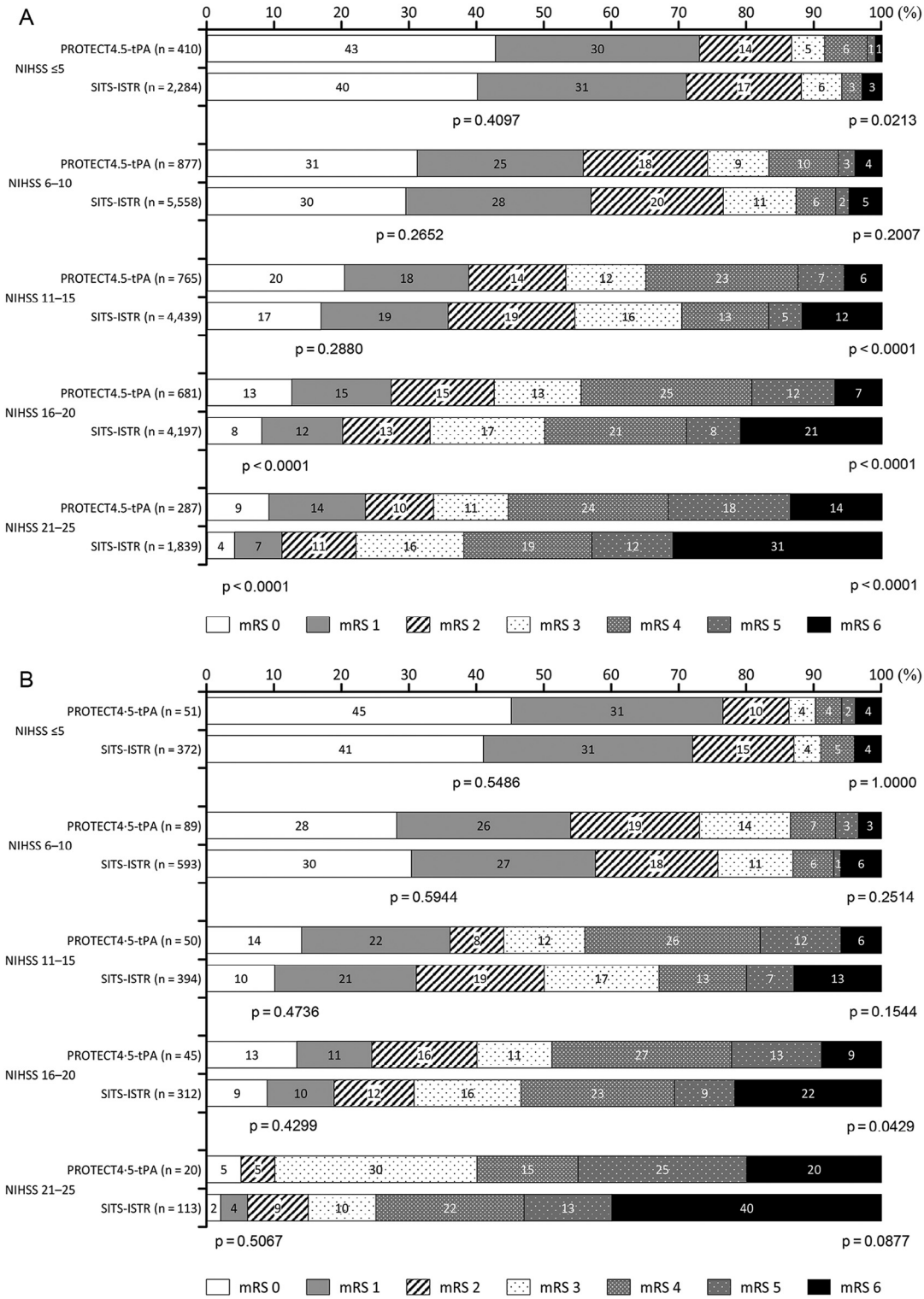

Figure 3. *Comparisons between PROTECT4.5-tPA (edaravone + tPA) and SITS-ISTR (tPA alone). Comparison of mRS at 3 months between PROTECT4.5-tPA and SITS-ISTR populations stratified by baseline NIHSS within (A) 3 hours of onset and (B) 3-4.5 hours after onset. Among patients with an NIHSS score ≥16, the proportion of patients with mRS 0-1 was higher in those receiving edaravone + tPA than in those receiving tPA alone. Incidence of sICH (according to SITS-MOST [C] and ECASS II [D] definitions) among PROTECT4.5-tPA and SITS-ISTR populations. The SITS-MOST definition was local or remote parenchymal hematoma type 2 (exceeding 30% of the infarct volume with a significant space-occupying effect) on the imaging scan obtained 22-36 hours after rt-PA treatment, plus neurologic deterioration, as indicated by NIHSS score ≥4 points higher than the baseline value or the lowest value between baseline and 24 hours, or hemorrhage leading to death. However, in PROTECT4.5, the size of the hemorrhage was not considered. The ECASS II definition was any hemorrhage with neurologic deterioration, as indicated by NIHSS score ≥4 points higher than the value at baseline or the lowest value in the first 7 days, or any hemorrhage leading to death. Abbreviations: ECASS, European Cooperative Acute Stroke Study; mRS, modified Rankin scale score; NIHSS, National Institutes of Health Stroke Scale score; sICH, symptomatic intracranial hemorrhage; SITS-ISTR, Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Registry; SITS-MOST, Safe Implementation of Treatments in Stroke-Monitoring Study; tPA, recombinant tissue plasminogen activator.*

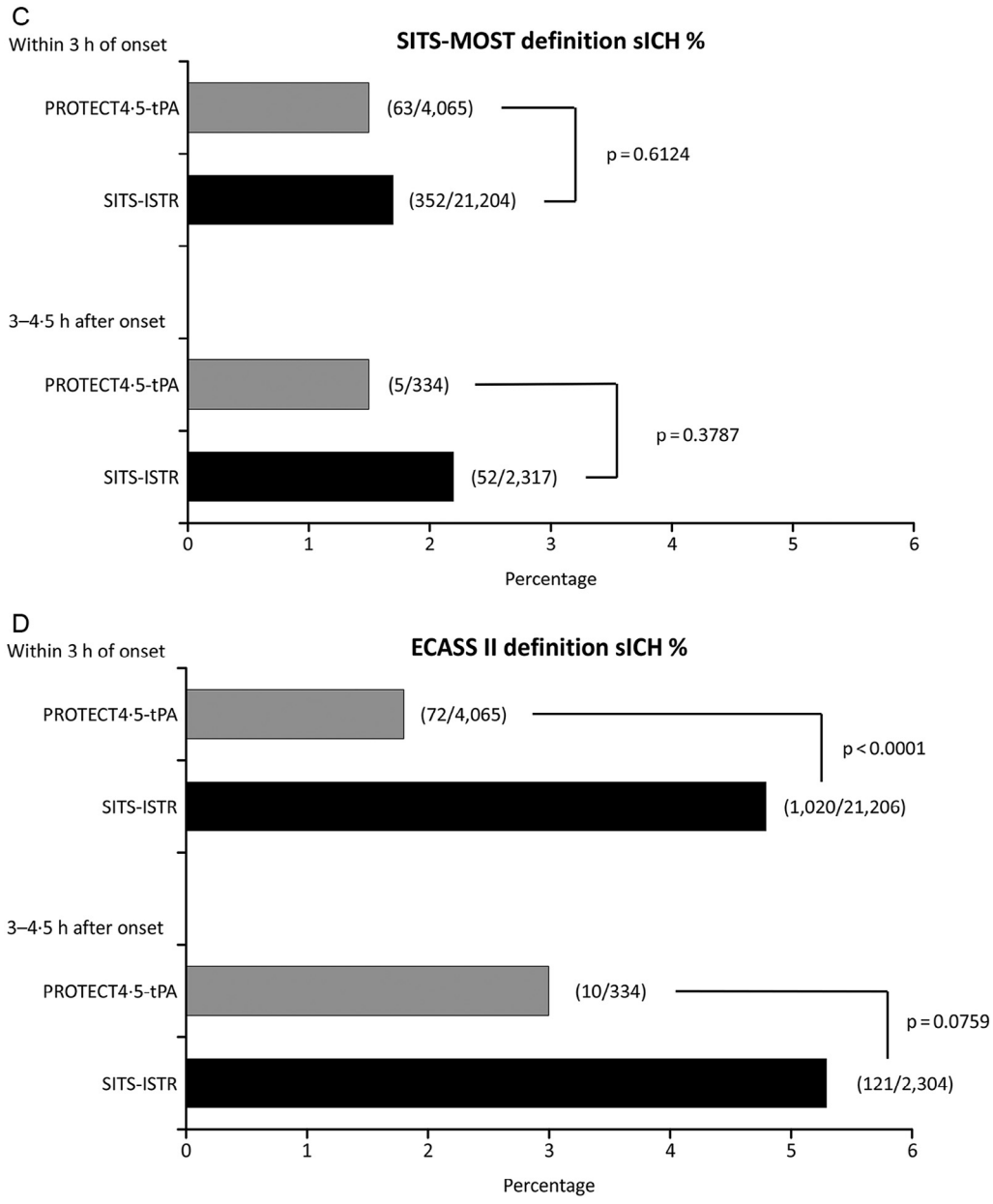

Figure 3. (*continued*)

unbiased adjusted estimates could be calculated to compare PROTECT4.5-tPA and SITS-ISTR populations, the findings suggest that edaravone + tPA may increase the proportion of patients having favorable outcomes and decrease the death rate compared with tPA alone, particularly in patients treated within 3 hours of onset and with an NIHSS score ≥16. There were no such differences in the proportion of patients having favorable outcomes (mRS 0-1) and death (mRS 6) between both groups (PROTECT4.5-tPA and SITS-ISTR) among those who had an NIHSS score ≤10. Similar results were obtained among patients treated within 3 hours of and 3-4.5 hours after onset, but the number of subjects in PROTECT4.5 was not large enough for comparison.

The incidence of sICH within 36 hours after tPA treatment (SITS-MOST definition) was lower in the PROTECT4.5-tPA populations than in SITS-ISTR among patients treated within 3 hours of onset. The same results were obtained in patients treated during 3-4.5 hours after onset. The SITS-MOST definition of sICH considers the hemorrhage size (parenchymal hematoma type 2) in brain imaging. However, in PROTECT4.5, the size of the hemorrhage was not accounted for. Thus, the quantification of sICH in the PROTECT4.5 population may have included even small hemorrhages if neurologic symptoms and signs deteriorated. When comparing the incidence of sICH within 7 days after tPA treatment (ECASS-II definition) between the two studies, the incidence was

significantly lower in PROTECT4.5-tPA than in SITS-ISTR in the 3-hour group ($P < .0001$).

The fact that the incidence of sICH in the PROTECT4.5-tPA populations was lower than that reported in SITS-ISTR may possibly be due to the lower dose of tPA (.6 mg/kg) used in Japan compared with that used in other countries (.9 mg/kg). The incidences of sICH within 36 hours after tPA treatment in Japanese clinical studies of tPA (.6 mg/kg) such as the Japan Alteplase Clinical Trial[11] (tPA alone), J-MARS[17] (tPA with or without edaravone), and PROTECT4.5 (edaravone + tPA) were 5.8%, 3.5%, and 1.6%, respectively, which suggests that edaravone + tPA may decrease the incidence of sICH.

Edaravone exerts a neuroprotective effect by suppressing the accumulation of lipid peroxidation products and oxidative DNA damage and eliminating the sequential inflammatory responses after ischemia and reperfusion.[18] This mechanism is thought to contribute to the clinical efficacy of edaravone and to the decrease in incidence of sICH when edaravone is added to tPA.

In the neurovascular unit, edaravone suppresses the dissociation of astrocyte endfeet from the basement membrane induced by tPA,[19] and prevents the expression and activation of matrix metalloproteinase-9 and oxidative stress damage caused by tPA treatment, which destroy the blood–brain barrier.[20,21] This mechanism is supposed to suppress the incidence of sICH. Edaravone added to tPA has been reported to improve functional outcome, improve the recanalization rate of occluded arteries, and decrease the incidence of intracranial hemorrhage.[22,23] Therefore, in the present study, the low incidence of sICH in the edaravone + tPA group is thought to be due to the suppression of sICH by protection of the neurovascular unit and blood–brain barrier.

The sICH after tPA treatment could deteriorate the final outcome of patients with cerebral infarction.[24] In the present study, the proportion of patients with sICH and mRS 5-6 at 3 months after onset with edaravone + tPA was 66% (82 out of 125). The incidences of sICH according to both the SITS-MOST and ECASS-II definition were lower in the PROTECT4.5-tPA population than those in SITS-ISTR. These results suggest that edaravone + tPA decreased the proportion of patients having unfavorable outcomes (mRS 5-6) by decreasing the incidence of sICH.

The present study has many limitations. First, this was an observational and nonrandomized study. Because patients were enrolled within 6 days after onset, there may have been selection bias as many cases of sICH occur within this period. Second, there may have been bias in the comparison between SITS-ISTR and PROTECT4.5-tPA population data because a complete adjustment could not be applied. Third, because the population size was notably smaller in PROTECT4.5-tPA than SITS-ISTR, the comparison of mRS stratified by baseline NIHSS scores should be interpreted with caution. Fourth, because the hemorrhage size was not considered in the PROTECT4.5-tPA population, based on the SITS-MOST definition of sICH, the incidence may have been lower than that in SITS-ISTR.

In conclusion, the efficacy and safety of edaravone combined with tPA and administered within 4.5 hours of AIS onset were demonstrated with numerically lower incidence of sICH after tPA administration and better outcomes.

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Appendix: Supplementary material

Supplementary data to this article can be found online at 10.1016/j.jstrokecerebrovasdis.2016.10.011.

References

1. Watanabe T, Egawa M. Effects of an antistroke agent MCI-186 on cerebral arachidonate cascade. J Pharmacol Exp Ther 1994;271:1624-1629.
2. Watanabe T, Tahara M, Todo S. The novel antioxidant edaravone: from bench to bedside. Cardiovasc Ther 2008;26:101-114.
3. Edaravone Acute Infarction Study Group. Effect of a novel free radical scavenger, edaravone (MCI-186), on acute brain infarction. Randomized, placebo-controlled, double-blind study at multicenters. Cerebrovasc Dis 2003;15:222-229.
4. Shinohara Y, Yamaguchi T. Outline of the Japanese Guidelines for the Management of Stroke 2004 and subsequent revision. Int J Stroke 2008;3:55-62.
5. Shinohara Y, Saito I, Kobayashi S, et al. Edaravone (radical scavenger) versus sodium ozagrel (antiplatelet agent) in acute noncardioembolic ischemic stroke (EDO trial). Cerebrovasc Dis 2009;27:485-492.
6. Toyoda K, Fujii K, Kamouchi M, et al. Free radical scavenger, edaravone, in stroke with internal carotid artery occlusion. J Neurol Sci 2004;221:11-17.
7. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359:1317-1329.
8. Wahlgren N, Ahmed N, Dávalos A, et al. Thrombolysis with alteplase 3-4.5 h after acute ischaemic stroke (SITS-ISTR): an observational study. Lancet 2008;372:1303-1309.
9. ESO. News update guidelines January 2009. Specific treatment: thrombolysis. Cerebrovasc Dis 2009;27:619-620.
10. Del Zoppo GJ, Saver J, Jauch EC, et al. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. Stroke 2009;40:2945-2948.
11. Yamaguchi T, Mori E, Minematsu K, et al. Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset. Japan Alteplase Clinical Trial (J-ACT). Stroke 2006;37:1810-1815.

12. Minematsu K, Toyoda K, Hirano T, et al. Guidelines for the intravenous application of recombinant tissue-type plasminogen activator (alteplase), the second edition, October 2012: a guideline from the Japan Stroke Society. J Stroke Cerebrovasc Dis 2013;22:571-600.
13. Ahmed N, Wahlgren N, Grond M, et al. Implementation and outcome of thrombolysis with alteplase 3-4.5 h after an acute stroke: an updated analysis from SITS-ISTR. Lancet Neurol 2010;9:866-874.
14. Ohta T, Waga S, Handa W, et al. New grading of level of disordered consciousness (author's translation). No Shinkei Geka 1974;2:623-627. [in Japanese].
15. Wahlgren N, Ahmed N, Dávalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet 2007;369:275-282.
16. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet 1998;352:1245-1251.
17. Nakagawara J, Minematsu K, Okada Y, et al. Thrombolysis with 0.6 mg/kg intravenous alteplase for acute ischemic stroke in routine clinical practice: the Japan post-marketing alteplase registration study (J-MARS). Stroke 2010;41:1984-1989.
18. Zang N, Komine-Kobayashi M, Tanaka R, et al. Edaravone reduces early accumulation of oxidative products and sequential inflammatory responses after transient focal ischemia in mice brain. Stroke 2005;36:2220-2225.
19. Yamashita T, Kamiya T, Deguchi K, et al. Dissociation and protection of the neurovascular unit after thrombolysis and reperfusion in ischemic rat brain. J Cereb Blood Flow Metab 2009;29:715-725.
20. Yagi K, Kitazato KT, Uno M, et al. Edaravone, a free radical scavenger, inhibits MMP-9-related brain hemorrhage in rats treated with tissue plasminogen activator. Stroke 2009;40:626-631.
21. Lukic-Panin V, Deguchi K, Yamashita T, et al. Free radical scavenger edaravone administration protects against tissue plasminogen activator induced oxidative stress and blood brain barrier damage. Curr Neurovasc Res 2010;7:319-329.
22. Kimura K, Aoki J, Sakamoto Y, et al. Administration of edaravone, a free radical scavenger, during t-PA infusion can enhance early recanalization in acute stroke patients–a preliminary study. J Neurol Sci 2012;313:132-136.
23. Takenaka K, Kato M, Yamauti K, et al. Simultaneous administration of recombinant tissue plasminogen activator and edaravone in acute cerebral ischemic stroke patients. J Stroke Cerebrovasc Dis 2014;23:2748-2752.
24. Strbian D, Sairanen T, Meretoja A, et al. Patient outcomes from symptomatic intracerebral hemorrhage after stroke thrombolysis. Neurology 2011;77:341-348.